PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)*	02 June 2005 (02-06-2005)
Applicant's or agent's file reference 064016356913	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/CA2005/000042	14 January 2005 (14-01-2005)	15 January 2004 (15-01-2004)

International Patent Classification (IPC) or both national classification and IPC
IPC(7): C07K 14/72; A61K 48/00; A61K 31/7098; A61K 39/395; A61K 38/17; A61K 45/00; G01N 33/566; G01N 33/567; C12Q 1/02; C12Q 1/68; A61P 15/06

Applicant
MOUNT SINAI HOSPITAL ET AL

1. This opinion contains indications relating to the following items :

[X]	Box No. I	Basis of the opinion
[ ]	Box No. II	Priority
[X]	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
[ ]	Box No. IV	Lack of unity of invention
[X]	Box No. V	Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement.
[ ]	Box No. VI	Certain documents cited
[ ]	Box No. VII	Certain defects in the international application
[X]	Box No. VIII	Certain observations on the international application

2. **FURTHER ACTION**
If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/CA Canadian Intellectual Property Office Place du Portage I, C114 - 1st Floor, Box PCT 50 Victoria Street Gatineau, Quebec K1A 0C9 Facsimile No.: 001(819)953-2476	Authorized officer Cynthia Brewer (819) 997-4921

Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] This opinion has been established on the basis of a translation from the original language into the following language ,which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of :

   a. type of material

      [X] a sequence listing

      [ ] table(s) related to the sequence listing

   b. format of material

      [X] in written format

      [X] in computer readable form

   c. time of filing/furnishing

      [X] contained in the international application as filed.

      [X] filed together with the international application in computer readable form.

      [ ] furnished subsequently to this Authority for the purposes of search.

3. [X] In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statement that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments :

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of :

[ ] the entire international application

[X] claim Nos. 1 to 16, and 20 to 38

because:

[X] the said international application, or the said claim Nos. 1 to 16, and 20 to 38
relate to the following subject matter which does not require an international preliminary examination *(specify)* :

Although claims 1 to 16, and 20 to 38 encompass either a method of treatment of the human/animal body or a method of doing business which this Authority is not required to examine under Rule 67.1 (iii) and Rule 67.1 (iv) of the PCT, the written opinion has been established on the basis of the alleged effects of PSF as a steroid receptor repressor.

[ ] the description, claims or drawings *(indicate particular elements below)* or said claim Nos.
are so unclear that no meaningful opinion could be formed *(specify)* :

[ ] the claims, or said claims Nos. are so inadequately supported
by the description that no meaningful opinion could be formed.

[ ] no international search report has been established for said claims Nos.

[ ] the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that :

the written form [ ] has not been furnished

[ ] does not comply with the standard

the computer readable form [ ] has not been furnished

[ ] does not comply with the standard

[ ] the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

[ ] See Supplemental Box for further details.

Box No. V **Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	13-29, 33, 39-43, 54	YES
	Claims	1-12, 30-32, 34-38, 44-53	NO
Inventive step (IS)	Claims	13-29, 33, 39-43, 54	YES
	Claims	1-12, 30-32, 34-38, 44-53	NO
Industrial applicability (IA)	Claims	1-54	YES
	Claims	None	NO

2. Citations and explanations :

Reference is made to the following documents:
D1: MCKENNA, N.J. et al. CELL 2002, Vol. 108, pages 465-474
D2: MATHUR, M. et al. MOL CELL BIOL. 2001, Vol. 21, No. 7, pages 2298-2311
D3: SHAV-TAL, Y. et al. FEBS LETTERS 2002, Vol. 531, pages 109-114
D4: CONDON, J.C. et al. PNAS 2003, Vol. 100, No. 16, pages 9518-9523
D5: HENDERSON, D. et al. AM J OBSTET GYNECOL. 2001, Vol. 185, pages 579-585
D6: SPITZ, I.M. STEROIDS 2003, Vol. 68, No. 10-13, pages 981-993

Novelty and Inventive Step - Articles 33(2) and 33(3) PCT

The problem to be solved by the instant application is the identification of an endogenous progesterone receptor (PR) modulator which may contribute to the functional withdrawal of progesterone. The present application discloses the identification of polypyrimidine tract-binding protein-associated splicing factor (PSF) as a PR interacting protein. The description discloses data to suggest that PSF regulates PR signal transduction (i.e. functionally withdraws progesterone) via two mechanisms: 1) binding with the progesterone receptor and targeting it for degradation via the proteosome and 2) interference of PR binding to its response element. In addition, PSF was shown to interact with the following additional steroid receptors, namely, glucocorticoid receptor and androgen receptor. The functional significance of the interaction is such that PSF acts as a repressor of PR, AR and GR transcriptional activity.

Firstly, it is known from document D1 that PR, GR and AR are all members of the nuclear receptor (NR) superfamily of transcription factors. NRs are divided into type I receptors, namely, the classical steroid receptors, such as, PR, GR and AR, and type II receptors such as thyroid hormone receptors (TR) and all-trans and 9-cis retinoic acid receptors (RAR and RXR).

Secondly, it is known from document D2 and D3 that PSF is a corepressor of thyroid hormone receptor (TR) and retinoid X receptors (RXR), both of which are type II members of the NR superfamily. However, PSF has not previously been identified or characterized as a repressor of steroid receptor signalling (i.e. type I NRs). Although, documents D2 and D3 disclose the capability of PSF to act as a repressor molecule of type II NRs, it would not have been obvious to a skilled person that PSF would interact with and modulate steroid receptors.

In addition, it is well established in the prior art that labor and delivery rapidly ensue if progesterone synthesis or actions are disrupted, i.e. functional progesterone withdrawal. For example, document D4 discloses that term labor is associated with a decrease in PR coactivators. Likewise, document D5 discloses that reduced binding of PR to its response element is associated with functional withdrawal of progesterone. Further, document D6 is a review paper pertinent to the subject of progesterone antagonists and progesterone receptor modulators.

Continued: see Supplemental Box

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made :

The description does not do not meet the requirements of Article 5 PCT because it does not contain sufficient technical information required to enable a skilled person to put all embodiments of the claimed method, pharmaceutical composition and use claims into practice. In particular, claims 1 to 12, 14, 30 to 32, 34 to 36, 38, and 44 to 53 encompass the administration of an otherwise undefined "agonist", "antagonist", "inhibitor", "agent" or a "compound or substance identified using a method of any preceding claim". The description does not disclose or identify any compound(s) which may be defined beyond an insufficient statement of the desired result to be achieved. In fact, a skilled person would be required to exercise undue experimentation in order to identify compounds which would be capable of the alleged effects.

Claim 1 contains a clerical error, namely, "polypyridimine" should read "polypyrimidine".

Claims 1 to 12 do not meet the requirements of Article 6 PCT. As currently formulated, these claims are broader in scope than the teachings of the description and lack clarity. In particular, the antagonist and agonist are merely defined as a result to be achieved. In fact, it is not clear if these compounds are modulators of the steroid receptor or PSF. Consequently, these chemical compounds are not adequately defined and cannot be unambiguously distinguished from any other steroid receptor modulators. Moreover, the description discloses the identification of PSF as a repressor of PR, AR and GR transcriptional activity and there is no support in the description for compounds broadly defined as an "agonist or antagonist thereof". In addition, in view of the description, it is not clear how a PSF complex *per se* can be used to modulate signal transduction mediated through a steroid receptor. Further, it is not clear if the steroid receptor within the PSF complex is the same as the receptor being subjected to modulation. Lastly, the nature of the modulation is not sufficiently set forth and, in view of the description, an essential feature of the alleged invention appears to be that PSF acts to repress transcriptional activity of PR, AR, and GR. Consequently, clarification is required.

Claims 1, 4, 5, 7, 8, 9, 13, 17, 23, 25, 29, 30, 31, 32, 34, 35, 36, 38, 39, 44, 45, 48, 49, and 51 do not meet the requirements of Article 6 PCT. Inclusion of the term "and/or" or "preferably" causes a lack of clarity.

Claims 13 and 14 do not meet the requirements of Article 6 PCT. The subject matter and scope of protection sought are not adequately defined. For example, in claim 13 the method steps set forth as "disrupting" and "promoting" are merely a result to be achieved and thus, lack clarity. Moreover, neither the "condition", "abnormality", "abnormal level of interaction" nor "activity" are sufficiently set forth.

Claim 17 does not meet the requirements of Article 6 PCT because it lacks clarity. This claim contains multiple alternatives which are not of similar nature and can not fairly be substituted for one another thus, the claim is ambiguous and difficult to construe. In addition, as noted above, the description provides support only for the function of PSF as a repressor of transcriptional activity of the steroid receptors, namely, PR, AR and GR.

Claims 21, 22, 24, and 37 do not meet the requirements of Article 6 PCT because they lack clarity. Specifically, for greater clairity, reference to preceding claims should be by number.

Claims 22 to 25 do not meet the requirements of Article 6 PCT. The intended "part" of the respective PSF polypeptide and progesterone receptor SEQ ID NOs are not adequately defined.

Claims 26 to 29 and 33 do not meet the requirements of Article 6 PCT. As currently formulated, these claims lack clarity as they are merely defined as a result to be achieved. The claims must include a step or series of steps which specify how "inhibiting", "stimulating" or "modulating" is achieved.

Claims 30 to 32 and 34 to 38 do not meet the requirements of Article 6 PCT. As currently formulated, these claims are broader in scope than the teachings of the description and lack clarity. In particular, the antagonist, inhibitor and agonist are merely defined as a result to be achieved. Consequently, these chemical compounds are not adequately defined and cannot be unambiguously distinguished from any other progesterone receptor modulators. Moreover, there is no support in the description for compounds broadly defined as an antagonist, inhibitor and agonist. In addition, in view of the description, it is not clear how a PSF complex *per se* can be used to achieve the alleged effect set forth in claim 38. Further, claim 38 should specify that the PSF complex is PSF-PR. Consequently, clarification is required.

Continued: see Supplemental Box

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of: Box V, 2. Citations and Explanation

Even though progesterone receptor modulators are described in the prior art the involvement of PSF in this signal transduction pathway has not been reported in the literature. Further, it would not have been obvious to a skilled person that PSF would contribute to the functional withdrawal of progesterone.

Nonetheless, claims 1-12, 30-32, 34-38, and 44-53 do not satisfy the criteria for novelty and inventive step. In view of the breadth of the scope claimed, these claims may be construed to include subject matter disclosed in document D6, namely, the use of progesterone receptor modulators in the modulation of a steroid receptor or process mediated by said receptor. In particular, these claims include the terms "antagonist" and/or "agonist" which are merely defined as a result to be achieved. Consequently, the intended antagonist and/or agonist cannot be unambiguously distinguished from any other progesterone receptor modulators, for instance, as disclosed in document D6. Moreover, applicant's attention is drawn to page 16, lines 12 to 31, of the instant description which defines an antagonist and/or agonist in "its broadest sense" to include any molecule which interacts with PR. Thus, claims 1-12, 30-32, 34-38, and 44-53 encompass old and known progesterone receptor modulators and old and known uses thereof.

In view of the above, as currently formulated, the subject-matter of claims 1-12, 30-32, 34-38, and 44-53 does not comply with Articles 33(2) and 33(3) PCT.

Novelty and inventive step for claims 13-29, 33, 39-43, and 54 and thus, compliance with Articles 33(2) and 33(3) PCT, is acknowledged based on the identification of PSF as a PR interacting protein and the function of PSF as a repressor of steroid receptor transcriptional activity.

Industrial Applicability - Article 33(4) PCT

Claims 17 to 19, and 39 to 54 appear to define subject matter that has industrial applicability under Article 33(4) of the PCT, based on the function of the PSF of the instant application as a repressor of steroid receptor transcriptional activity.

For the assessment of claims 1 to 16, and 20 to 38 on the question of whether or not they define subject matter that has industrial applicability, no unified criteria exists in the PCT. Further, the patentability of said claims can depend upon their formulation. Although the methods *per se* defined in claims 1 to 16, and 20 to 38 relate to subject matter which this Authority is not obliged to examine under Rule 67.1 (iii) and Rule 67.1 (iv) of the PCT, the use of PSF referred to therein as a steroid receptor modulator appears to represent subject matter that has industrial applicability.

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of:

Continuation of: Box VIII, Certain observations on the international application

Claim 35 is missing a period.

Claims 39 to 42 do not meet the requirements of Article 6 PCT because they lack clarity. In particular, it is not clear how the detection of a ubiquitously expressed protein, namely, PSF can be useful to identify pre-term labor or the onset of labor. Rather, it would appear that the subject matter set forth in claim 43 would be an essential feature of these claims.

Claims 44 to 52 do not meet the requirements of Article 6 PCT. In particular, the claimed pharmaceutical composition and use are not adequately defined. As currently formulated, these claims are broader in scope than the teachings of the description and lack clarity. For example, these claims recite an otherwise undefined "agonist", "antagonist", "inhibitor", "agent" or a "compound or substance identified using a method of any preceding claim". The description does not disclose or identify any compound(s) which may be defined beyond an insufficient statement of the desired result to be achieved. In fact, it is not clear if these compounds are modulators of the steroid receptor or PSF. Consequently, these chemical compounds are not adequately defined and cannot be unambiguously distinguished from any other steroid receptor or progesterone receptor modulators. In addition, these claims contain multiple alternatives which are not of similar nature (i.e. agonist versus antagonist) and can not fairly be substituted for one another thus, the claim is ambiguous and difficult to construe. As noted above, the description discloses the identification of PSF as a repressor of PR, AR and GR transcriptional activity. In addition, as noted above, it is not clear how a PSF complex *per se* can be used to achieve the alleged effect(s). Clarification is thus required.

Claim 53 does not meet the requirements of Article 6 PCT. The claimed kit is not adequately defined. In particular, no components or reagents are specified thus, it is not clear what is encompassed by the claimed kit. In addition, it is noted that not all preceding claims are method claims and thus, preceding claims should be referred to by number.